Poster I-47

Drug Target Protein Prediction Using Biopanning and Computational Screening of Combinatorial Peptide Libraries

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Discovering the target protein or DNA that tightly binds to a drug or other biologically active molecule can be compared to finding of a needle in a haystack. Contemporary drug design uses a number of computer based strategies to find this needle. At the San Diego Supercomputer Center and the Rebecca and John Moores UCSD Cancer Center we have developed a combined experimental and computational approach to find possible drug target proteins. The program HMM-ELONGATOR predicts putative protein targets from a set of short peptides selected from a combinatorial library by phage display biopanning for affinity to the drug molecule.

The results of biopanning experiments are sets of short peptides that show binding activity to an immobilized drug molecule. These peptides are assumed to be related to fragments of an active protein. Reconstructing the putative protein can be a difficult task because of the statistical uncertainty associated with aligning many of short, poorly overlapping sequences. The difficulty is increased by the fact that any single short peptide is at best a small part of a typical binding site. Furthermore, the libraries often contain peptides that are not parts of any protein. Many of these bind to the probe molecule. Use of these peptides in multiple alignments increases the noise level in the data. The statistical significance of the alignments is already weak because of the short (7-12 residues) peptides. The challenge of these experiments to obtain longer peptides that can be used much more reliably in identifying the entire sequence of potential protein targets.

The program HMM-ELONGATOR addresses these problems through use of a more discriminating probabilistic model. Recently this program identified two probable target proteins, topoisomerase I and c-myc, for the anticancer drug Irofulven (HMAF) from phage display binding data. Independently of these findings we created a pharmacophore model of irofulven. Using our molecular docking program DOT and the pharmacophore model suggests that irofulven binds to Topoisomerase I differently from other Topoisomerase I inhibitors, and that this binding disrupt the contact of Topoisomerase I with DNA. Both Topoisomerase I and c-myc have since been experimentally confirmed as irofulven targets by *in vivo* synergy studies with other known inhibitors of these proteins (Kelner et al., 2001).

Reference

Kelner MJ, Tsigelny I, Sharikov Y, Ten Eyck LF, Elyadi AN, McMorris TC. Phage display panning of irofulven identifies potential intracellular targets. Proc AACR-NCI-EORTC. Intl. Conf. Molecular Targets and Cancer Therapeutics, Miami Beach, FL, 2001